REMARKS

Status of the Claims

The application as filed contained claims 1 – 23. Responsive to a restriction requirement, including species election, applicants have elected to pursue claims 1 – 3, 5 – 12, and 17 – 19. Applicants, therefore, hereby confirm the election of these claims for further prosecution.

The Action has rejected claims 1 – 3, 5 – 12, and 17 – 19 under various statutory grounds. Currently no claims stand allowed. Applicants have added new claims 24 and 25 by amendment herewith. Support for these claims is amply provided in the specification as filed, particularly in Example 3. Consequently, no new matter has been added to the application.

Applicants respectfully submit the following remarks and urge that all of the claims stand in a condition for allowance, which action is respectfully requested.

Objection to Drawings

The Action has indicated an objection to the drawing for Figure 1 on the basis that the legend fro the ordinate access is not legible. Applicants hereby acknowledge said objection and further indicate that, upon receipt of a Notice of Allowance for the instant application, will submit a corrected drawing addressing the noted problem.

Rejections of the Claims

35 U.S.C. §102(b) (Ross *et al.*)

The Action has rejected claims 1-3, 7-9, 12, and 17-19 as allegedly being anticipated by Ross *et al., Pain* **84**: 421-428 (2000) ("Ross"). The Action has characterized Ross as disclosing methods of administering sub-analgesic amounts of morphine and oxycodone followed by an observation of a marked antinociceptive synergy. The Action concluded that "Ross *et al.* intrinsically reduces the risk associated with the administration of opioid analgesics in patients," and reads on the cited claims. Applicants respectfully traverse.

Although the data disclosed in Ross *et al.*, in accord with the Action's characterization, disclose the antinociceptive synergy arising from compositions comprising oxycodone and morphine, it is clear that this result was the sole investigative goal of the work. The reference provides no substantive data on the impact of the synergistic analgesic compositions on expected

side effects such as respiratory depression, which impact is at the core of the invention disclosed and claimed in the instant application. Indeed, the very analgesic synergy disclosed in the Ross *et al.* reference would lead one of ordinary skill in the appropriate art to expect a concomitant level of synergy with respect to side effects of this sort. The widely-accepted reference, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed., New York: McGraw-Hill (2001) (see copy of Chapter 23, "Opioid Analgesics," attached hereto as Exhibit A) unequivocally states, on page 579, in the context of the use of mixed opioid compositions to reduce the occurrence of side effects such as respiratory depression, that "for the same degree of analgesia, the same intensity of side effects will occur." (Emphasis added.)

The results disclosed in the instant application clearly provide an unexpected benefit from mixed-opioid compositions not predicted by the prior art. The disclosure of Ross *et al.* is directed to the foundation observation that analgesic synergy is possible with compositions comprising mixed μ- and κ-opioid agonists. Any comments directed to possible implications on side effects such as respiratory depression are mere speculation - - speculation, as indicated above, that flies in the face of accepted prior art wisdom. The proof of an unexpected decrease in side effects such as respiratory depression, in a synergistically analgesic mixed-opioid composition, has never been disclosed until the instant application. Thus, the instant application is the first disclosure to establish that it is possible to achieve both analgesia and a reduction in respiratory depression with a composition of mixed μ- and κ-opioid agonists.

The Action, in rejecting claims 1 – 3, 7 – 9, 12, and 17 – 19 over Ross *et al.*, stated that "the method disclosed by Ross et al. intrinsically reduces the risk associated with the administration of opioid analgesics in patients," further citing to disclosed dosing ratios of oxycodone to morphine. Applicants respectfully disagree. To begin with, Applicants point out that the dosing ratios of the compositions for which data is provided in Ross *et al.* do not overlap with those of disclosed and claimed in the instant application, particularly in light of newly added claims 24 and 25. Nor is the mass ratio of one opioid to the other in the composition a minor issue. Looking at extremes of relative loading, even without a clear picture of the mechanism of synergy between the μ- and κ-opioid agonists, it is logical that, as a composition approaches a preponderance of one or the other opioid component, then the opportunity for synergy decreases, until the composition begins to function as if it contains only a single opioid component. Given that each of the single opioid components is present at a sub-analgesic level,

the clinical result would be ineffectiveness for its intended analgesic purpose. Thus, a threshold question arises: what is the minimum ratio of μ- and κ-opioid agonists necessary to create sufficient synergy to achieve the primary analgesic effect? Perhaps more importantly, in terms of the instant invention, is at what relative component ratios is it possible to achieve both analgesic synergy and a reduction in side effects such as respiratory depression?

It is unlikely that data yet exists on where the absolute limits of composition capable of analgesic synergy lie. The disclosure of Ross *et al.* addresses where within those limits analgesically effective compositions may be formulated. However, there is nothing disclosed in the Ross *et al.* reference (or any other reference cited in the Action) on where within those extremes of composition is it possible to achieve both analgesic synergy and a reduction in respiratory depression.

Looking at the specific compositions disclosed in Ross *et al.*, the first route of administration involved intracerebroventricular (i.c.v.) delivery of the compositions directly into the test animal's cerebrospinal fluid *via* a surgically-inserted cannula. The compositions delivered by this route are described as comprising 40 nmol of oxycodone and 15 nmol of morphine, when delivered in combination. Converting these amounts to appropriate mass quantities in grams, based on literature values for the molecular weight of the hydrochloride salts of both active ingredients, the resulting mass ratio of oxycodone to morphine is approximately 2.5:1 (2.464:1). This is a ratio this is substantially beyond that disclosed and claimed in the instant application. However, Applicants point out that this particular route of administration (directly bypassing the blood/brain barrier) significantly affects any observed results from this composition and cannot be, as would be recognized by one of ordinary skill in the relevant art, extrapolated to systemic routes of delivery. The Ross *et al.* reference specifically acknowledges this (see, for example, p. 422).

In looking at the other compositions disclosed in the reference, the relative mass loadings of oxycodone and morphine are considerably different from the instant invention. For intraperitoneal (i.p.) delivery, the compositions comprised 571 nmol of morphine and 621 nmol of oxycodone. Converting to mass units, this represents a 1:1 mass ratio between the components. For subcutaneous (s.c.) delivery, as referenced in the Action, compositions are described in terms of the ED_{50} (providing half maximal response) dose determined from the

individual doses of oxycodone and morphine. Figure 3 of the reference depicts the data on which the authors based this determination. The ED_{50} result was calculated to be 2.8 mg/kg oxycodone and 8.5 mg/kg morphine. Using these figures, relative mass ratios for the compositions administered to the test animals resulted in oxycodone to morphine ratios ranging from 1:9 to 1:1. The mass ratios in these compositions, again, are significantly different from those disclosed and claimed in the instant application. The significance of this difference is emphasized by the recognition in the art (see *Goodman and Gilman's*, attached; Ross *et al.*) that CNS effects such as respiratory depression are mediated through the μ-opioid receptors, those to which morphine binds. If looked to at all for utility in diminishing respiratory depression (counter to then art-accepted principles), the teachings of Ross *et al.* would be undesirable for such effect.

On this basis, Applicants respectfully submit that the cited reference does not adversely impact the patentability of the claims in questions and urges immediate allowance of same.

35 U.S.C. §102(b) (Smith *et al.* WO '438)

The Action has rejected claims 1 – 3, 5, 7 – 12 and 17 – 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* Applicants respectfully traverse.

As addressed above in respect to the disclosures of the Ross *et al.* reference, the disclosure of the Smith *et al.* reference is directed solely to the analgesic synergy arising from compositions comprising mixtures of μ- and κ-opioid agonists. The reference does not disclose any objective data supporting a reduced occurrence of side effects, such as respiratory depression, from administration of the compositions. As also pointed out above, prior to the instant application, the accepted wisdom in the prior art was that any composition displaying an increased analgesic effect would also display an accompanying increase in undesirable side effects (such as respiratory depression). A mere suggestion that it "may be possible" with the disclosed compositions to achieve both analgesia and reduced side effects falls far short of the standard necessary for an anticipating disclosure. As for inherency, contrary to the assertion of the Action, the cited reference fails to disclose any data that would enable one of skill in the art to both recognize and to be able to select from among the wide range of compositions disclosed as displaying analgesic synergy those specific compositions that would also be capable of definitively reducing the occurrence of undesirable side effects such as respiratory depression.

Furthermore, determining the specific mass loadings of the disclosed compositions (see Examples 1 and 4) results in a 2.5:1 oxycodone:morphine ratio for i.c.v. administration, and ratios in the range of 1:9 to 1:1 oxycodone:morphine for systemic administration (see discussion of Ross *et al.*, above). Data from other Examples likewise discloses compositions heavily weighted toward higher morphine:oxycodone mass ratios. These compositions are substantially different from those claimed in the instant application.

Thus, the cited reference provides no objective teaching that the disclosed compositions, in fact, result in reduced side effects, nor do the specific compositions encompass the relative mass loadings of oxycodone and morphine disclosed and claimed in the instant application. On this basis, Applicants respectfully suggest that the cited reference does not adversely impact the patentability of the claims and urges the Examiner to move the application to allowance.

35 U.S.C. §102(b) (Smith *et al.* '072 patent)

The Action has rejected claims 1 – 3, 5, 7 – 12 and 17 – 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* ('072 patent). Applicants respectfully traverse.

As with the Smith *et al.* (WO '438) reference discussed immediately above (which reference is a foreign counterpart to the instant reference and, thus, shares a common disclosure), the cited reference falls far short of anticipating the instant claims. The reference's disclosure is limited solely to the analgesic synergy between μ- and κ-opioid agonists and fails to provide any teaching establishing that the disclosed compositions are capable of reducing the occurrence of side effects such as respiratory depression. Nor does the reference disclose or even suggest how to select from among the numerous compositions disclosed those that would be capable of both providing analgesic synergy and a reduction in undesirable side effects. On this basis, Applicants respectfully submit that the cited fails reference fails to anticipate the instant claims and requests the examiner to withdraw the instant rejection.

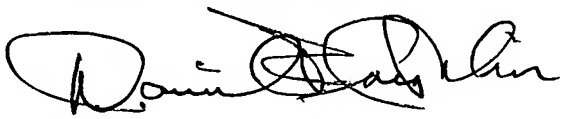
35 U.S.C. §103(a) (Smith *et al.* WO '438)

The Action has rejected claims 1 – 3, 5 – 12 and 17 – 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* (WO '438). Applicants respectfully traverse.

The Action has cited the reference on the basis that the reference allegedly motivates one of skill in the art to substitute oxymorphone for morphine in the compositions disclosed therein.

Applicants point out that oxymorphone, like morphine, is a μ-opioid agonist. In light of this, the arguments presented above with respect to references disclosing combinations of morphine and oxycodone apply equally well to compositions comprising oxymorphone and oxycodone. Furthermore, as addressed in previous communications with the Examiner in response to earlier-issued restriction requirements, the structural backbone of various opioids and derivatives does not control the physiological properties of such species relevant to the instant invention. Thus, the structural similarity between morphine and oxymorphone, to the extent relevant at all, far from rendering the rejected claims obvious, merely serves to validate the logic of previously proffered arguments directed to morphine compositions disclosed in other cited references. On the basis of structural similarities, there would be no motivation to substitute one μ-opioid agonist for another, at similar mass loadings (adjusted for molecular weight differences) in a composition designed to minimize the side effects known to be regulated through μ-opioid receptors. On this basis, and for the reasons stated above with respect to other bases of rejection, Applicants respectfully submit that the claims as they now stand are patentable over the cited reference and in a condition for allowance. Applicants respectfully request such action.

Respectfully submitted,



Daniel F. Coughlin
Registration No. 36,111